Study Title:

Improving Outcomes for Patients With Sleep-Disordered Breathing and Insufficient Sleep (RESTORE)

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Protocol
Improving Outcomes for Patients with Sleep-Disordered Breathing and Insufficient Sleep

Recruitment and Screening

We will recruit 495 participants from two accredited sleep disorders centers: 1) The Sleep Disorders Center at Detroit Receiving Hospital and 2) The Center for Sleep and Respiratory Disorders in Novi. All two centers adhere to the standards of the American Academy of Sleep Medicine (AASM), and studies are interpreted by Board Certified Sleep Medicine Physicians. Using processes previously approved by our IRB, we will use two main recruitment strategies. First, study announcements will be posted in the clinical laboratories with contact information for the research staff. Individuals who call will be screened by telephone. Second, we will send patients referred for evaluation of SDB a brief letter briefly explaining the study and an opportunity to "opt out" of future contact. We will obtain a waiver of consent to review medical records of potential participants to determine if they meet basic inclusion/exclusion criteria. Individuals who do not opt out will be contacted by phone and screened for basic eligibility. Interested individuals meeting basic criteria on phone screening will be invited to a face-to-face visit where informed consent will be obtained, additional screening measures will be completed and baseline assessments will begin. A study physician will review diagnostic tests to determine the utility of the documented AHI for study purposes. Those with an AHI from an overnight PSG within the past 5 years may not be asked to repeat their sleep study. We anticipate that at least 345 (70%) of participants will meet all randomization eligibly criteria, and we plan to randomize 176 participants to one of the 2 treatment arms.

Covid-19 Precautions: In lieu of in-person visits, we may mail the informed consent document and HIPPA authorization form to eligible interested patients prior to the consent appointment, which may be conducted using a WSU approved telehealth platform or telephone. Patients who agree to participate may return the signed consent and HIPPA form by prepaid mail or drop them off at the Mott Center. If patients prefer to drop off the consent and HIPPA form, research staff may arrange to meet the patient in the Mott parking lot or inside the building. In lieu of in-person visits, we may use the REDCap e-Consent tool to complete and obtain the consent document including the HIPPA authorization form.

The *Inclusion Criteria for enrollment* are*:*

1) over age 18 years
2) diagnosed with mild to moderate SDB (AHI of 5-30).

Additional *Criteria for randomization* will be:

3) ESS score $\geq$ 6 or PVT $\geq$ 4 lapses
4) Total sleep time <7 hours at least 5 nights per week, based on baseline sleep diary.

The *Exclusions criteria* are:

1) Current use of PAP or oral appliance therapy for SDB
2) Severe respiratory or cardiovascular disease (e.g., ventilatory failure, congestive heart failure)
3) A recent health event that may affect sleep (e.g. recent surgery or hospitalization)
4) Current alcohol or substance use disorder (<90 days sobriety) or significant unstable psychiatric comorbidity (e.g., suicidal ideation, psychosis)
5) Pregnancy or within 6 months post-partum
6) Commercial drivers and individuals at risk for motor vehicle accidents (MVA) or ESS>18
7) significant comorbid sleep disorders (e.g., severe insomnia, narcolepsy); and
8) central sleep apnea (defined as central apnea/hypopnea index >5, and >50% of total AHI).
9) use of sedative-hypnotic medications higher than the maximum acceptable therapeutic dose range.

Measurements

Baseline assessments will include measures needed to assess inclusion/exclusion criteria and gather baseline values for study outcomes. Measures were selected based on strong psychometric properties, while being mindful of participant burden. Outcome measures will be repeated at post-treatment and at 1 and 3-months follow-up (see **Table 1**).

Table 1: Study variables to address each specific aim.

Objective metrics	Measurement instruments	Key Variables	Base-line	1mo f/up	3mo f/up
Sleep disordered breathing	AHI from polysomnography	AHI*	X		
Daytime alertness	Psychomotor Vigilance Test (PVT)	# lapses	X	X	X
Mean 24-hour ambulatory blood pressure	24-hour blood pressure monitoring	Mean 24 hour AMBP	X	X	X
Mean automated office-based blood pressure	Oscillometric blood pressure measurement	Mean AOBP	X	X	X
Endothelial Function	Fingertip plethysmography (EndoPAT)	RHI	X	X	X
Sleep duration	Wrist actigraphy	TST†	X	X	X
Patient-reported measures					
Daily sleep diary	AASM Consensus sleep diary	TST*†	X	X	X
Subjective sleep quality	Pittsburgh Sleep Quality Index (PSQI)	Total score	X	X	X
Insomnia severity	Insomnia Severity Index (ISI)	Total score*	X	X	X
Daytime sleepiness	Epworth Sleepiness Scale (ESS)	Total score*	X	X	X
Daytime fatigue	Multi-dimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) Fatigue Severity Scale (FSS)	Total score	X	X	X
Health-related quality of life	SF-36	Component scores	X	X	X
Disease-specific Quality of Life	Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10) Sleep Apnea Quality of Life Index (SAQLI)	Total score	X	X	X
Symptoms of depression and anxiety	Patient Health Questionnaire- 9 (PHQ-9) GAD-7	Total score	X	X	X

*to assess inclusion/exclusion criteria; †Also used during STE intervention to track adherence. AHI=apnea hypopnea index; AMBP=ambulatory blood pressure; AOBP: ambulatory office-based blood pressure; TST=total sleep time; RHI=reactive hyperemia index

Description of objective measures

Polysomnography (PSG) for SDB diagnostic testing. Polysomnography (PSG) will be used to diagnose SDB. Physiologic signals will include electrooculogram, submental electromyogram, electrocardiogram, and electroencephalogram (EEG; C4M1, O1M2, and F4M1). Respiratory effort and rib cage/abdominal synchrony will be measured using Respiratory Inductance Plethysmography. We will follow current AASM scoring criteria, including the scoring of hypopnea if there is a ≥3% drop in oxygen saturation from pre-event baseline, or the event is associated with an EEG arousal.

To minimize participant burden, individuals who have a recent, full-night clinical PSG typically will not be asked to repeat the PSG for research purposes. Individuals who have not completed a full-night PSG for clinical purposes and those who have had a health change since their clinical PSG will be asked to have a full-night PSG within the research study. The recruitment sites are accredited laboratories that adhere to AASM scoring guidelines, and Dr. Chowdhuri or Rowley (medical directors) will over-read all clinical studies for enrolled patients to assure consistency with study protocols and procedures. Based on review of clinical data for these two centers from 2017, we anticipate that 50% of participants will have a viable AHI from clinical PSG. Key Variable: AHI

Wrist actigraphy will be used to objectively measure total sleep time (TST). Participants will wear an actigraph (Actiwatch 2, Minimitter/Respironics, Bend, OR) on the non-dominant wrist for one week. The actigraph is a small watch-sized device useful in longitudinal, naturalistic assessment of sleep patterns. [3,4] Actigraphs contain accelerometers which measure movement. In general, movements below an established threshold is interpreted as sleep while high activity is interpreted as wakefulness. Commercially available software uses validated algorithms to determine minute-by-minute sleep vs. wake. Actigraphy has been validated in numerous studies, evidence-based guidelines direct use of this technology, and it is commonly used to objectively monitor adherence to sleep schedules prior to in-laboratory studies. We have developed highly standardized research procedures and protocols for use and scoring of actigraphy, and we have trained, experienced members of our research team to apply these protocols. In our research work with patients who have sleep disorders, actigraphy has been well-tolerated, with less than 5% missing data. We will analyze actigraphy data defining "night" and "day" based on sleep diary-reported bedtimes and rising times [3]. Key variable: mean nighttime total sleep time (TST).

Psychomotor Vigilance Test (PVT). [5,6]We propose to use the PVT as the main outcome measure. PVT has been validated as a performance test to ascertain the presence and severity of sleepiness and has been shown to be responsive to sleep loss, subjective sleepiness, and circadian rhythm. Specifically, the PVT measures

simple reaction time (RT) to a visual cue, delivered at random inter-stimulus intervals, varying from 2 to 10 seconds. The standard PVT is 10 minutes long. The primary tested variable is the lapse, defined as a reaction time>500ms. A lapse is thought to represent a "micro-sleep" or instability in the state of wakefulness. Key Variable: total number of lapses during the 10-minute test.

Blood pressure monitoring., We will use ambulatory BP monitoring (AMBP) as out primary measure. Ambulatory BP monitoring captures BP fluctuations over a 24-hour period, defining an individual's BP profile while awake and asleep. Ambulatory BP is a better predictor of CVD risk than conventional office-based resting BP measurements and has emerged as the preferred approach for diagnosis and monitoring of therapeutic effectiveness [7-10]. In this study, ambulatory BP will be monitored over a 24-hour period (SpaceLabs 90217). Average 24-hour BP levels as well as daytime (6am-10pm; 2X/hour) and nocturnal BP (10pm-6am; 1X/hour) levels will be assessed [11-13]. Values for the 24-hour period will be averaged (mean 24-hour ambulatory BP) as well as during each time (daytime and nighttime). All activities will be documented during that period via a participant log developed and used by Drs. McGowan and Levy in prior work. Participants will be instructed to perform similar activities during post-testing data collection to standardize BP recordings. They will be asked to refrain from activities that may cause the cuff to come off the arm, or where they cannot easily pause during cuff inflation. These activities will again be documented by the participant, and confirmed following the monitoring session with assessment staff. In addition to ambulatory BP monitoring, we will record automated office-based BP (AOBP) using the BpTRU device. By using both measures, we will be able to assess the ability of in-office BP assessment to detect changes observed in with 24-hour monitoring. Key variable: mean 24-hour blood pressure.

Peripheral Arterial Tonometry (PAT). We will explore endothelium-dependent dilation in response to reactive hyperemia, utilizing peripheral arterial tonometry (PAT; EndoPAT, Itamar Medical Ltd., Caesarea, Israel) [14-15]. There is evidence that PAT measurement of endothelial function predict CVD events over a 6-year follow-up period. Participants will be instructed to fast for eight hours, refrain from caffeine, alcohol, and tobacco, and avoid exercise for eight hours prior to testing. Using fingertip plethysmography, the PAT device continuously measures digital pulse wave amplitude (PWA) during three phases: a quiet baseline period, 5-min forearm occlusion, and reactive hyperemia following cuff release. PAT testing is operator independent and post-test analysis is largely automated. The test will be performed following the manufacturer's guidelines, in a quiet, dimmed, and temperature controlled room as previously described with upper arm occlusion at 250 mmHg. The hyperemic response will be analyzed using the device's proprietary software and the reactive hyperemia index (RHI) will be calculated from pre- and post-occlusion measurements by the device software using previously described methods [14].

Description of Patient-reported measures

Daily diaries. Participants will complete daily sleep diaries based on the American Academy of Sleep Medicine Consensus Sleep Diary [33], which we adapted using a cognitive interviewing process[34] for patients with sleep apnea. The baseline diary will be used to confirm that the participant sleeps less than 7 hours per night at least 5 nights per week. Diaries will be used during the sleep extension intervention to track progress, and repeated at post-treatment and at the 3-month follow-up. Key variable: mean and nightly TST.

Sleep questionnaires. The Pittsburgh Sleep Quality Index (PSQI) assesses sleep quality and disturbances over the past month. The PSQI is sensitive for distinguishing normal and abnormal sleepers and has good test-retest reliability. We will use the 3-factor scoring, which has been shown to have superior psychometric properties [32]. The Insomnia Severity Index (ISI) is a 7-item instrument using Likert-type scales to measure severity of insomnia symptoms. The ISI correlates well with scores on the PSQI (r=.67), and with sleep diary measures (r's=.32-.91). This will be used to exclude individuals with severe insomnia disorder.

Daytime symptom questionnaires. The Epworth Sleepiness Scale (ESS) will be used as the main outcome measure. The ESS is a self-administered questionnaire with 8 questions to address the propensity to "doze off" under a variety of situations. We will also use the Multi-dimensional Fatigue Symptom Inventory-Short Form (MFSI-SF)) [16,17]to measure the general, physical, emotional and mental manifestations of fatigue. The MSFSI-SF is a 30-item scale which assess key components of the full MFSI. Flinders Fatigue Scale (FFS) will also be used to measure the general, physical, emotion and mental manifestations' impact on fatigue. The FSS is a 7 item scale used to measure general symptoms of fatigue.

Quality of life. The Medical Outcomes Study Short-Form-36 (SF-36) [18] is a 36-item health-related quality of life questionnaire that includes eight domains: physical functioning; role limitations due to physical health; role limitations due to emotional health; role limitations due to emotional problems; energy/fatigue; emotional well-being; social functioning; pain; general health; and a single item that identifies perceived change in health status.

Each domain scale is scored from 0% to 100%. The recently published recommendations for standard research assessment in insomnia trials include the SF-36 as a recommended/essential measure of health-related quality of life. We will also use the Functional Outcomes of Sleep Questionnaire (FOS-Q-10) [19.20] to assess disease-specific quality of life. The FOS-Q-10 is a 10-item scale that the impact of sleepiness on daily function and has shown to improve with effective treatment of SDB. We will also use the Calgary Sleep Apnea Quality of Life Index (SAQLI) to measure disease-specific quality of life. The SAQLI is a 35-item questionnaire that evaluates 4 domains of quality of life associated with sleep apnea: daily functioning, social interactions, emotional functioning, symptoms, and treatment-related symptoms (for individuals using PAP therapy).

Patient Health Questionnaire- 9 The Patient Health Questionnaire-9 (PHQ-9) [21] is a 9-item depression module in the PHQ, which is part of the Primary Care Evaluation of Mental Disorders (PRIME-MD) suite of evaluation tools. The PHQ-9 will be used to identify individuals with severe depression or suicidal ideation who may not be appropriate for the study.

The **Generalized Anxiety Disorder-7** (GAD-7) is a component of the PRIME-MD that was developed for evaluation of Generalized Anxiety Disorder (GAD). This 7-item scale has sensitivity and specificity above 0.80 for GAD, panic disorder, social anxiety and PTSD. The GAD-7 total score will be used to measure anxiety symptoms.

In lieu of in-person visits, we may administer questionnaires using a WSU approved telehealth platform. Participants may receive and return the questionnaires, sleep diary, actigraph, AMBP machine, and AMBP journal and other study documents or equipment by prepaid mail or by meeting research staff at the Mott Center.

Randomization and blinding

Prior to randomization, the final set of inclusion/exclusion criteria will be reviewed at a weekly staff meeting. We have minimized exclusions to the extent possible to increase the generalizability of our findings to clinical practice. Individuals who complete baseline assessments and meet inclusion/exclusion criteria will be randomly assigned to one of two interventions in a 1:1 ratio: STE (n=88) and PAP (n=88). Randomization procedures will follow CONSORT guidelines. [1] Randomization will be blocked by sleep study (Split Night PSG or Full night PSG) and sex (men/women). This blocked randomization scheme will help us to ensure equal numbers of men and women across groups so sex differences in treatment response can be explored. This approach will also reduce the likelihood that individuals at age extremes will disproportionately be assigned to one of the groups. The randomization sequence will be generated and maintained by Dr. Ghosh (statistician).

Interventions

Each intervention (STE and PAP) will involve 4 weekly sessions with a trained interventionist. Each program is described below in Tables 2-3. To avoid the possibility of contamination, we will have separate research staff members perform each of the interventions. First, all sessions will be recorded, and selected sessions (all sessions for the first 5 participants per group, and at least one session per month) of each intervention arm will be reviewed by Dr. Martin to assist with interventionist training and to ensure the integrity of the intervention over the course of the study. Second, interventionists will also maintain a session-by-session check list of information covered, participant progress and recommendations made. These "progress notes" will be reviewed during weekly supervision meetings with Dr. Martin. Third, participants will complete brief treatment expectancy (end of session 1) and credibility questionnaires (end of session 4) as well to ensure that each treatment is viewed as an acceptable option for patients with mild to moderate SDB. Forth, extensive intervention process measure (attendance, understanding, recommendations made at each session) will be documented and reviewed at weekly supervision meetings.

Sleep Time Extension (Table 2): We will test a 4-session sleep time extension (STE) program modeled after programs developed and tested in prior work. The program involves 4, 60-minute sessions including the following components: a) education about normal sleep, the impact of sleep loss and the benefits of increasing sleep time; b) identification of factors that motivate the individual to increase sleep time; c) goal setting and progress monitoring using sleep diaries; d) discussion of strategies for sustained behavior change. The program includes exercises and strategies drawn from Cognitive Behavioral Therapy[22] and Motivational Interviewing[23].

Table 2: Sleep Extension Condition: Education plus motivational enhancement plus participant self-monitoring (n=88)

Week	Title	Components/Topics	Motivational Strategies	Homework
Week 1	Restoring your natural sleep drive	Education: sleep drive, and recognition of sleepiness signs (vs. fatigue) Sleep hygiene education and behavioral targets (screen exposure, diet, exercise, substance use)	Linking insufficient sleep to patient values and goals; understanding behavior change	Sleep diary; increase TIB; address sleep disruptive factors
Week 2	Restoring your clock	Education: Circadian rhythms Discussion of schedule regularity and behavioral strategies to improve	Discuss pros/cons of regular sleep schedule. Link to patient values and goals	Reduce variability in sleep schedule, further increase TIB, continue healthy sleep habits
Week 3	Sleep and stress	Education: impact of stress on sleep and alertness Identify specific stressful situations near bedtime (or in bedroom) Cognitive strategies to address bedtime worry	Identify difference between continuing with insufficient sleep vs. sufficient sleep over the long-term	Sleep dairy, implement wind-down time at end of night, regular sleep schedule, further increase TIB, continue healthy sleep habits
Week 4	Personalized plan for healthy sleep	Education: personalized strategies to maintain healthy sleep duration	Link continued adequate sleep to personal goals and values	n/a

PAP Therapy with adherence program: PAP therapy remains the recommended first-line treatment for SDB, regardless of severity[25]. Participants randomized to the PAP therapy arm will receive PAP therapy consistent with their severity and type of SDB. Dr. Badr will prescribe PAP therapy based on the sleep study findings. If a PAP titration study was conducted in the clinical lab, the prescription (i.e., pressure settings) will be based on clinical recommendations. If no PAP titration study was done, and there are no contra-indication, auto-PAP will be used.

Since low PAP adherence is an important consideration in evaluating the potential effects of the treatment, a 4-session PAP adherence program, which begins the day PAP therapy is initiated, will be used (**Table 4**). This program is based on our prior work demonstrating increased PAP adherence using behavioral and motivational enhancement techniques (see preliminary data) [26]. PAP use will be monitored remotely using modem-based transmission of PAP machine usage data.

Table 3: PAP adherence program for participants assigned to the PAP arm (n=88)

Week	Title	Components/Topics	Homework
Week 1	Restore your airways	Education: Information about sleep apnea and PAP therapy Motivational strategies: linking PAP use to patient values and goals	Sleep and PAP use diary to track progress toward goals
Week 2	Troubleshooting and goal setting	Education: Common challenges to PAP use; patient-centered solutions Motivational strategies: set PAP therapy use goals; identify benefits (if any) that may be linked to PAP	Sleep and PAP use diary to track progress toward goals
Week 3	Self-management of sleep apnea	Education: introduce concept of chronic disease management Motivation strategies; increase self-efficacy with examples	Sleep and PAP use diary to track progress toward goals
Week 4	Long-term PAP use	Education: planning for ongoing treatment (e.g., frequency of follow up visits, equipment maintenance) Motivation strategies: increase self-efficacy, set long-term goals.	Sleep and PAP use diary to track progress toward goals

In lieu of in-person visits, randomized participants may be mailed the session materials or PAP device and supplies prior to their scheduled appointment with the study trained interventionist. The interventionist may conduct the education sessions using a WSU approved telehealth platform if in-person visits are not feasible.

Follow-up assessments (1-month "post-treatment" and 3-month follow-up)

As shown in **Table 1** (above) After the 4-week intervention period (approximately 1 month after randomization), select baseline measures will be repeated. These will be repeated at 3-months follow-up to assess the main study outcomes. Staff members who complete all follow up assessments will be blinded to group assignment. To improve retention, participants will be offered compensation for follow-up assessments, regardless of whether they complete the intervention.

Transition to clinical care after follow-up

After the 3-month follow-up visit, participants will be scheduled for a face-to-face follow-up visit with the sleep disorders clinic from which they were recruited. At that point, the participant will discuss all available, appropriate treatment options with their healthcare provider, including alternative treatments for SDB, if appropriate. Drs. Rowley and Chowdhuri (medical directors) will assist with the transition of patients into the clinical care pathway at the conclusion of the study.

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